

SALVAGE THERAPIES FOR SCLC

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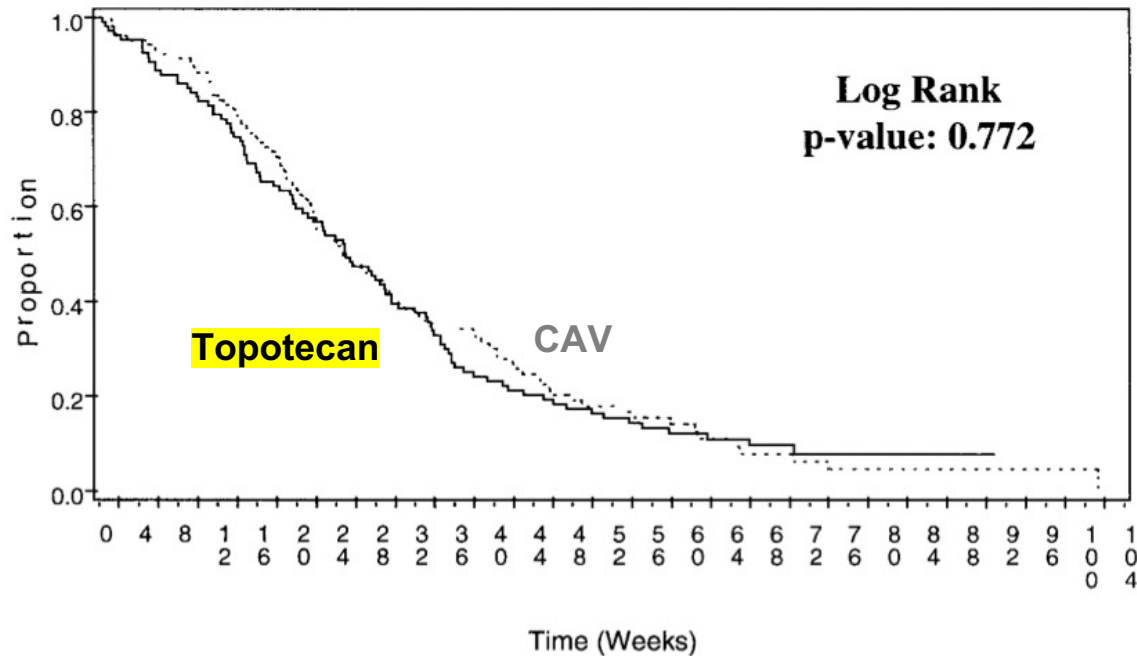


Presented by



Topotecan: The Reluctant Standard

- Similar response rates: topotecan 24.3% and CAV 18.3% ($P = .285$).
- Overall median survival was 25.0 weeks for topotecan and 24.7 weeks for CAV ($P = .795$).
- Significant GI & hematologic toxicities (G4 neutropenia/NF, G3/4 anemia, G3/4 thrombocytopenia)



Photography Credit: Theresa Colbert
@Goinkbrokeranch

von Pawel J, Schiller JH, Sheperd FA, et al. *J Clin Oncol*. 1999.

Relapsed SCLC: Decades of Disappointment

A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer

EF Smit¹, E Fokkema¹, B Biesma², HJM Groen¹, W Snoek³ and PE Postmus²

Table 3 Response, time to progression and survival

	Number of patients
Complete response	0
Partial response	7 (29%; 95% CI 12–51%)
Stable disease	5
Progressive disease	9
Early death	2
Toxic death	1
Response duration	Median (range) days 108 (64–243)
Time to progression*	Median (range) days 65 (33–243)
Survival**	Median (range) days 100 (23–262)

*Seven patients non-evaluable (three patients with disease progression after one course; two ED and one TD); **three patients non-evaluable (two ED, one TD).

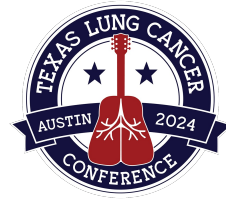
DISCUSSION

One of the key problems in the management of SCLC is to overcome the emergence of drug-resistant relapses. Few drugs or drug combinations are capable of effecting tumour regression in the setting of an early relapse, i.e. within 3 months off induction chemotherapy. Platinum-based combinations are probably most effective in this situation, but response rates and response duration of such regimens are disappointingly low (Andersen et al, 1990).

New drugs with new mechanisms of action are clearly needed for these poor prognosis patients.

Smit EF, et al. *Br J Cancer*. 1998.

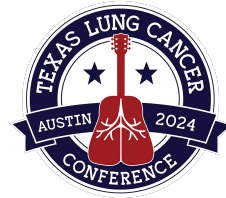
Relapsed SCLC: A Call for Help



“The search for better treatments in relapsed SCLC is thus a high priority.”

- *Joan Schiller, M.D. (1997)*

Schiller JH. *Semin Oncol.* 1997.



Relapsed SCLC: A Benchmark to Beat

ORIGINAL ARTICLE

A Systematic Analysis of Efficacy of Second-Line Chemotherapy in Sensitive and Refractory Small-Cell Lung Cancer

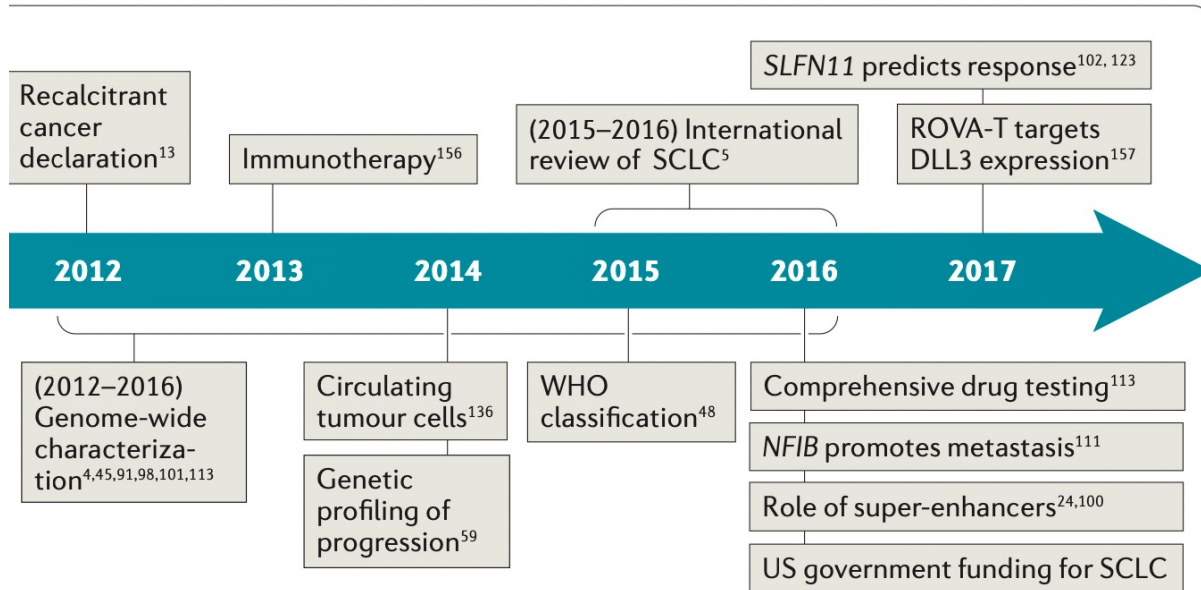
Taofeek K. Owonikoko, MD,# Madhusmita Behera, MS,* Zhengjia Chen, PhD,† Chandar Bhimani, MD,*
Walter J. Curran, MD,‡ Fadlo R. Khuri, MD,* and Suresh S. Ramalingam, MD**

- Meta-analysis of 21 studies between 1984-2011
- 1,692 pts (53.9% platinum-sensitive, 46.1% platinum-resistant)
- Response rate by platinum-sensitivity: **27.7%** (-sensitive, S) vs. **14.8%** (-resistant, R) $P = .0001$
- Median overall survival: **7.7** (S) vs **5.4 months** (R) $P = .0035$

Owonikoko TK, Madhusmita B, Chen Z, et al. *J Thorac Oncol.* 2012.

Relapsed SCLC: The Second Golden Age

The Second Golden Age



Photography Credit: Theresa Colbert @Goinbrokeranch

Gazdar AF, Bunn PA, Minna JD. *Nat Rev Cancer*. 1997.

Relapsed SCLC: A Beacon of Hope

• Lurbinectedin

- Selective inhibitor of transcription & TME

Phase 2 single-arm basket trial

- 105 pts with relapsed SCLC (2 or 3L)
- 3.2 mg/m² dose IV q3weeks
- 1^o endpoint: Overall response rate = **35.2%**
- Platinum-response: **45.0%** (S) vs **22.2%** (R)

Accelerated FDA approval (June 2020)

Confirmatory Phase 3 in SCLC (ongoing)

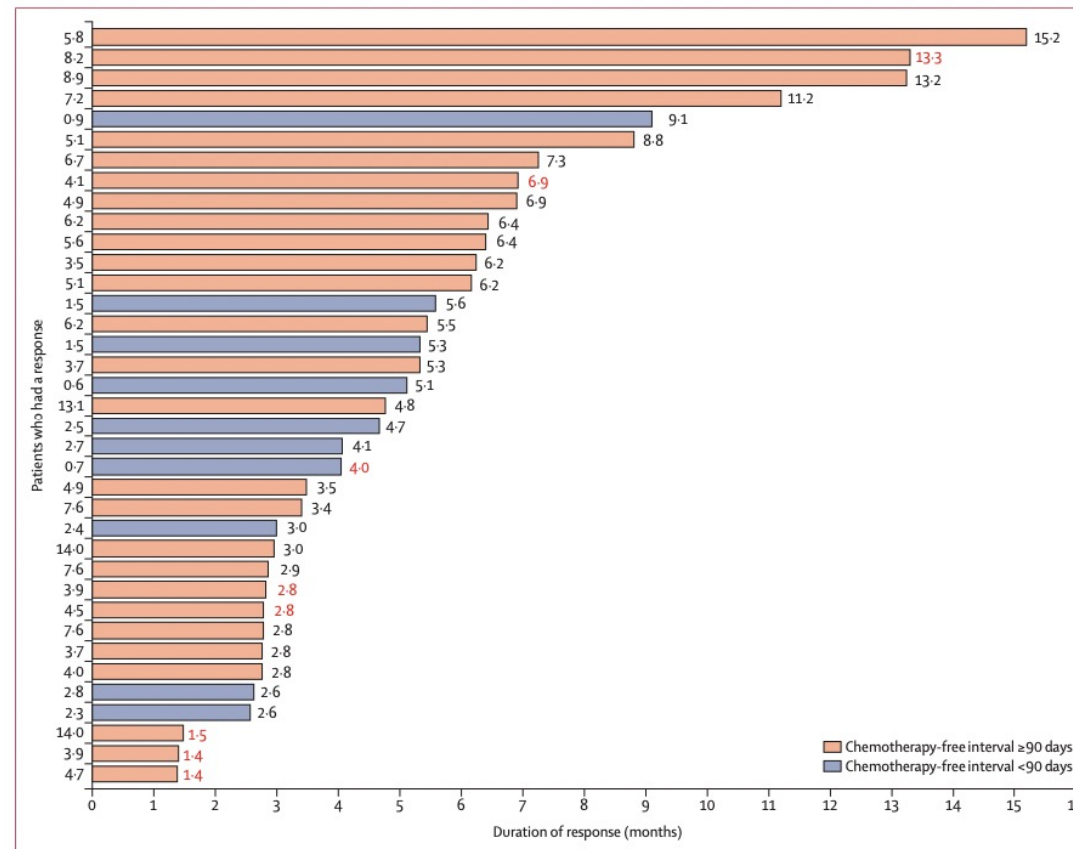


Figure 1: Duration of response by investigator assessment
 Each bar represents a patient with SCLC who responded to treatment (n=37). Data shown on the left of each bar are the chemotherapy-free interval (months); data shown on the right of each bar are the duration of response (0 is the time of starting response). Data in red font refer to eight patients censored at the cutoff date: seven with no documented progression (under follow-up) and one who discontinued treatment due to an investigator's decision and then received further therapy. SCLC=small-cell lung cancer.

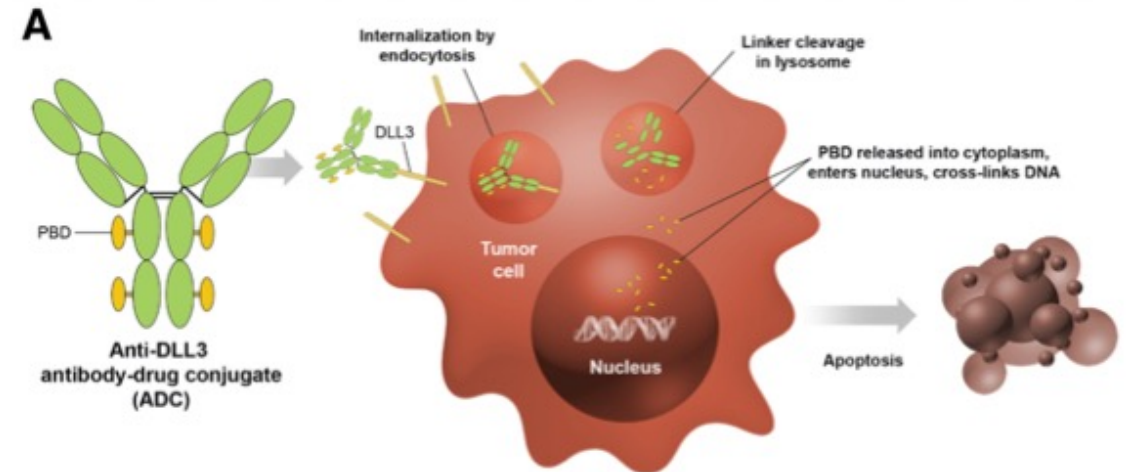
Relapsed SCLC: All That Glitters...

DLL3 Antibody Drug Conjugate (ADC)

➤ ROVA-T

- TAHOE: 2L (vs Topotecan)
- MERU: 1L Maintenance (vs BSC)

➤ *Failed to demonstrate benefit*



Owen DH, Griffin MJ, Bailis JM, et al. *J Hematology & Oncology*. 2019.

All That Glitters Is Not Gold: The Story of Rovalpituzumab Tesirine in SCLC

Dipesh Uprety, MD, FACP,^a Jordi Remon, MD, PhD,^b Alex A. Adjei, MD, PhD^{c,*}

Relapsed SCLC: Finding the Silver (DLL3) Lining

DLL3 BiTEs

DLL3/CD3 IgG-like bispecific T-cell engagers

- **Tarlatamab**
- **BI 764532**

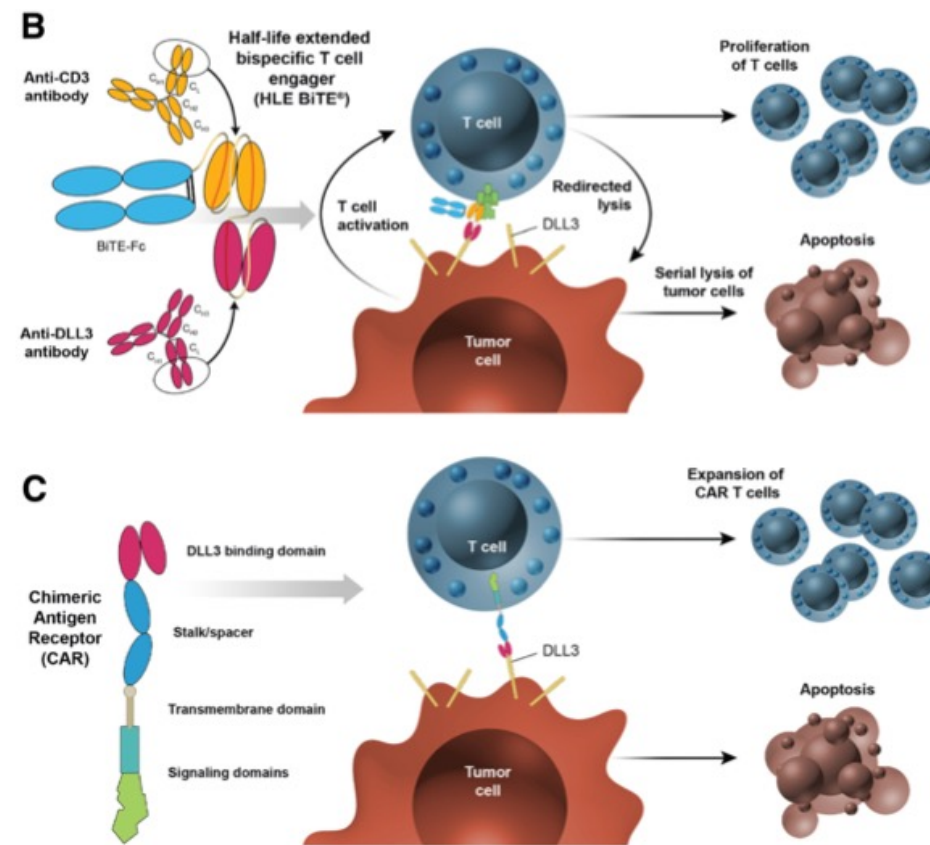
DLL3 TriTE

DLL3/CD3 IgG-like/albumin tri-specific T-cell engager

- **HPN328**

DLL3 CAR T Cell Therapy

- **AMG 119**



Owen DH, Griffin MJ, Bailis JM, et al. *J Hematology & Oncology*. 2019.

Relapsed SCLC: Finding the Silver (DLL3) Lining

➤ Tarlatamab/AMG 757

Phase 1 DeLLphi-300 (NCT03319940)

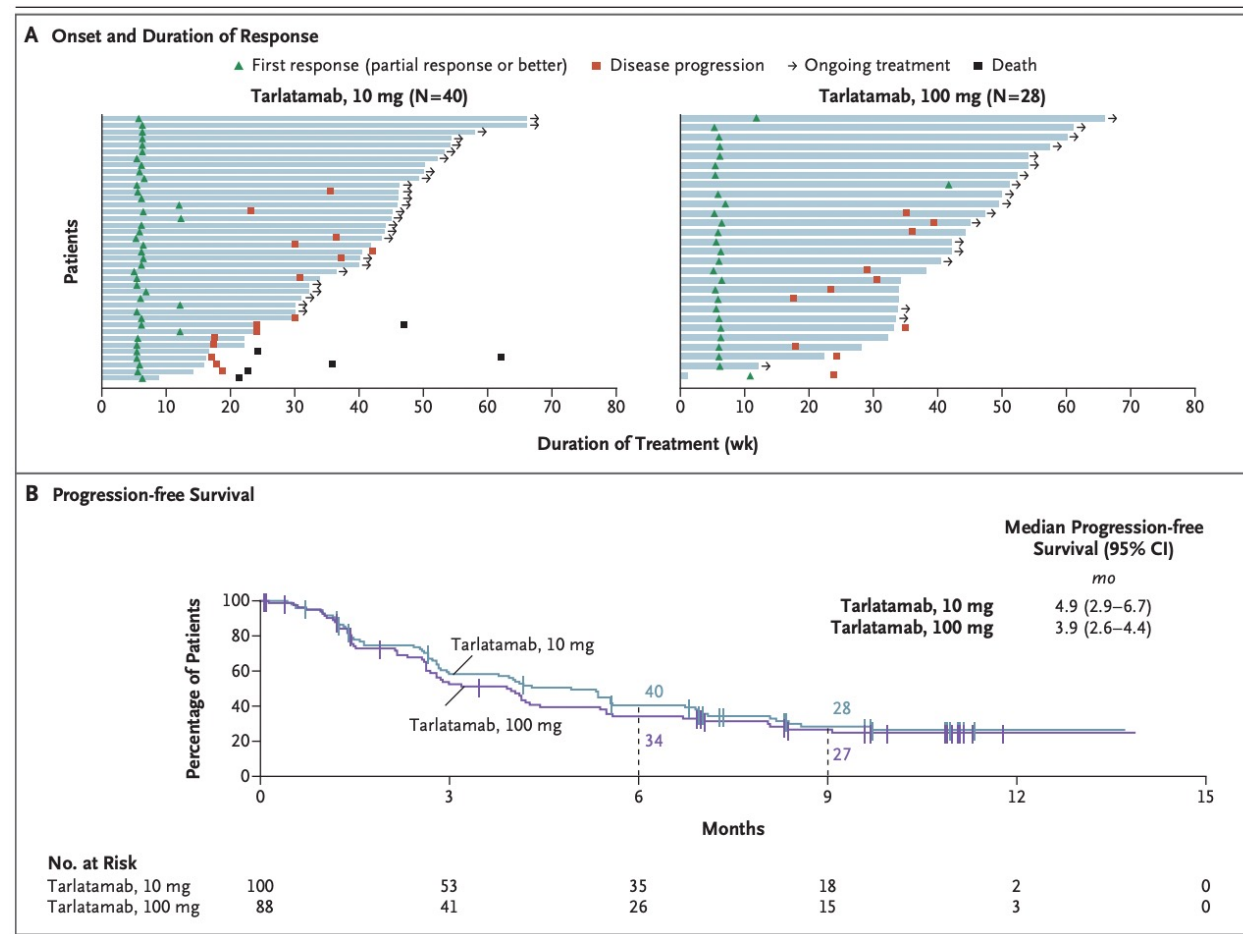
- 107 pts: 73 pts (dose exp), 34 pts (100 mg)
- ORR: 23.4%, mDOR: 12.3 months
- mPFS: 3.7 months, mOS: 13.2 months

Phase 2 DeLLphi-301 (NCT05060016)

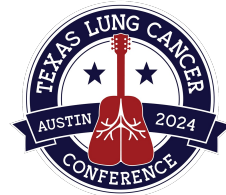
- 220 pts: 10 mg or 100 mg cohorts q2w
- ORR: 40% (10 mg), 32% (100 mg)
- mDOR: >6 months in 59% pts

Phase 3 DeLLphi-304 (NCT05740566)

- 700+ pts: 2L vs SOC (lurbi, topotecan)
- 1° Endpoint: OS (active)



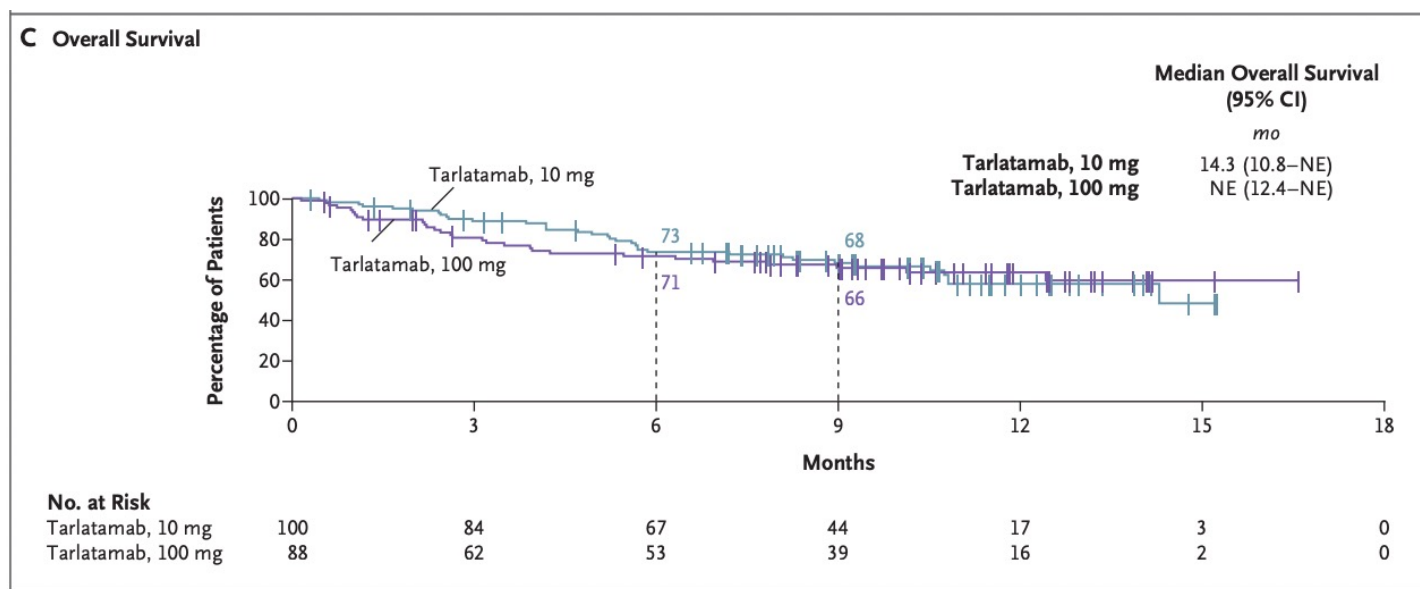
Ahn M-J, Cho BC, Filip E, et al. *NEJM*. 2023.



Relapsed SCLC: Finding the Silver (DLL3) Lining

➤ Tarlatamab/AMG 757

Stay Tuned: Under FDA Priority Review designation, the Prescription Drug User Fee Action (PDUFA) date for Tarlatamab is **June 12, 2024**



“Despite the many challenges, the results offer renewed hope to our patients.”
-Pilar Garrido, MD PhD (2023)

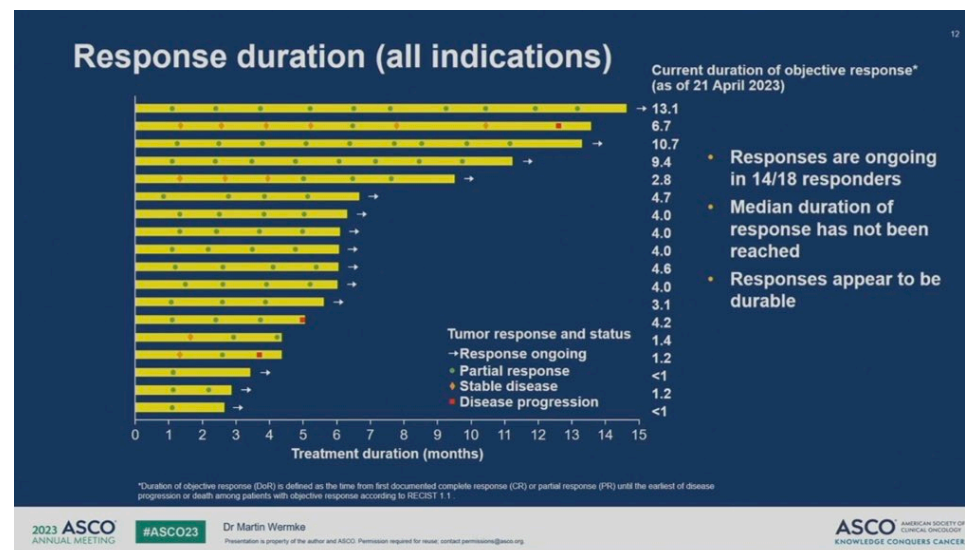
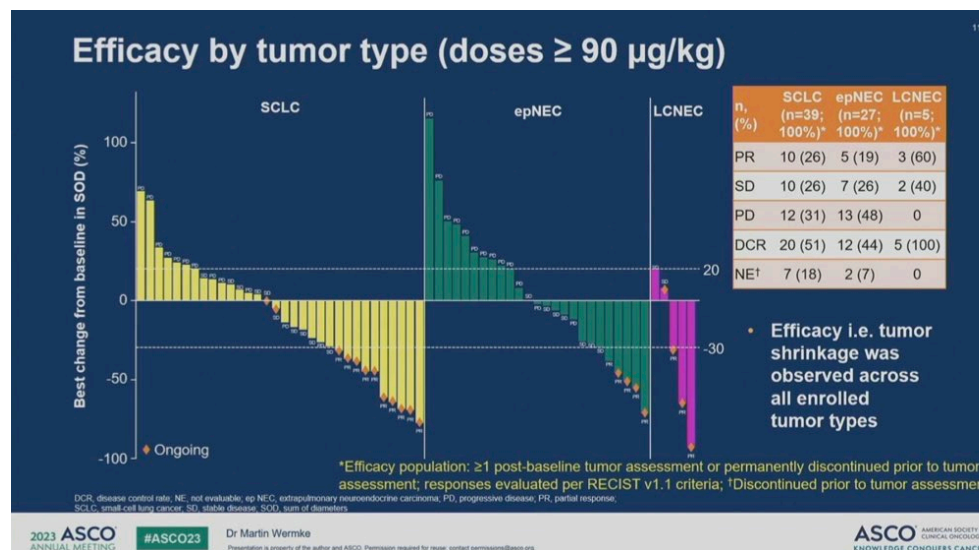
Ahn M-J, Cho BC, Filip E, et al. *NEJM*. 2023.

Relapsed SCLC: Finding the Silver (DLL3) Lining

➤ BI 764532

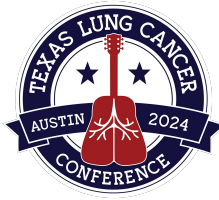
Phase 1 first-in-human trial (NCT04429087)

- 107 pts: relapsed SCLC, LCNEC, epNEC
- 1° endpoint: MTD (not reached)
- 2° endpoint: PK/ORR (ORR: 25%, DCR: 52%)
- TRAE: Low-grade CRS, neurotoxicity



Presented by Dr. Martin Wermke at ASCO 2023

Relapsed SCLC: Finding the Silver (DLL3) Lining



➤ BI 764532

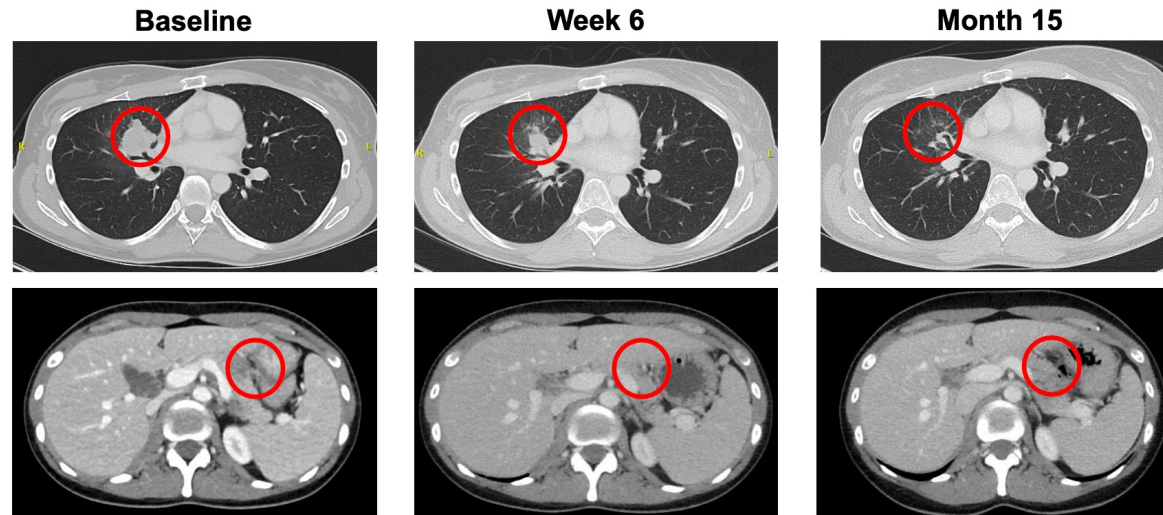
Phase 1 first-in-human trial (NCT04429087)

IASLC |  2023 World Conference
on Lung Cancer

SEPTEMBER 9-12, 2023 | SINGAPORE



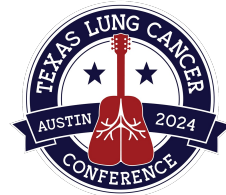
Response to treatment in a patient with SCLC who had previously relapsed 3 months after radiochemotherapy



Prof. Dr Martin Wermke, TU Dresden University of Technology, Germany

11.

Presented by Dr. Martin Wermke at WCLC 2023

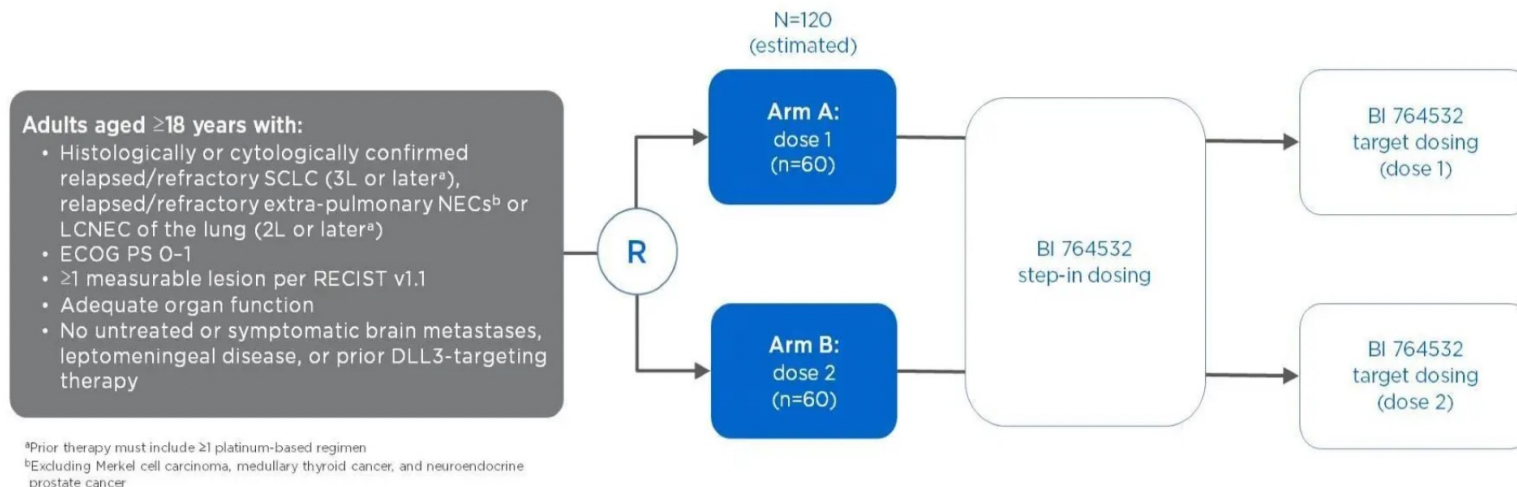


Relapsed SCLC: Finding the Silver (DLL3) Lining

➤ BI 764532

Phase 2 1438-0005/DAREON-5 (NCT05882058)

- 3L SCLC, 2L LCNEC & epNEC (active)



Endpoints

Primary	OR, TEAEs during the on-treatment period
Secondary	DOR, PFS, DC, OS, PROs, TEAEs leading to discontinuation

Start Date

September 2023

Status

~~Not yet recruiting~~

Estimated completion:
July 2025

Slide courtesy of BoehringerIngelheim.com

Relapsed SCLC: Light at the End of the Tunnel

Antibody Drug Conjugates

➤ Trop2: Sacituzumab Govitecan (SG)

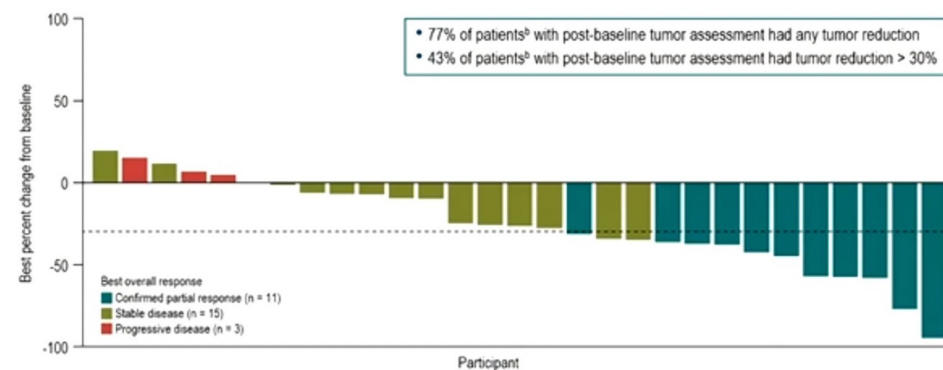
TROPiCS-03 - Phase 2 Basket Trial (NCT03964727)

- 30 pts: 2L ES-SCLC
- 10 mg/kg IV D1 and D8 q21days
- 1° endpoint: ORR: 37%
- DOR at 6 months: 63%
- DCR (confirmed CR, PR, SD): 87%
- Most common TEAE: any grade diarrhea, ↓ ANC

Efficacy by investigator assessment

Efficacy by INV ^a	ES-SCLC N = 30 ^b
ORR [Confirmed CR + PR] (95% CI), %	37 (20-56)
BOR, n (%)	
Confirmed PR	11 (37)
SD	15 (50)
PD	3 (10)
DCR [Confirmed CR + PR + SD] (95% CI), %	87 (69-96)
CBR [Confirmed CR + PR + SD ≥ 6 months] (95% CI), %	40 (23-59)
Median DOR (95% CI),^{c,d} months	6.3 (2.7-NR)
DOR rate at 6 months (95% CI),^{c,d} %	63 (14-89)

Best percent change from baseline in target lesions^a



Includes patients enrolled on or before 27 April 2023. RECIST v1.1. Response Evaluation Criteria in Solid Tumors version 1.1. ^aBy investigator assessment per RECIST v1.1. ^bPercentages were calculated using the total number of patients (N = 30).



Presented by: Afshin Dowlati, MD

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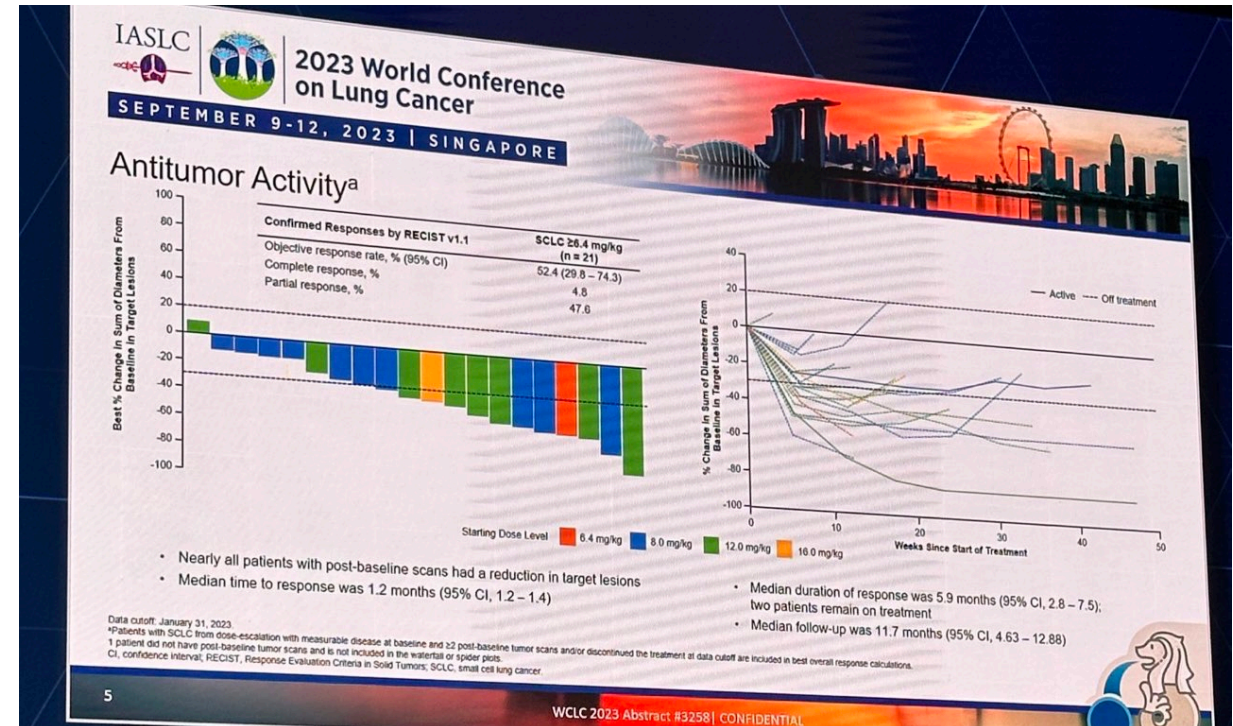
Presented by Afshin Dowlati MD at ESMO 2023

Relapsed SCLC: Light at the End of the Tunnel

➤ Ifinatamab Deruxtecan “I-DXd” DS-7300

Phase 1/2 (NCT04145622)

- 22 pts SCLC: unselected for B7-H3
- >6.4 mg/kg
- ORR: 52.4% (4.8% CR, 47.6% PR)
- Median time to response: 1.2 months
- mDOR: 5.9 months
- TEAEs: any (100%), ILD (1), pneumonitis (1)

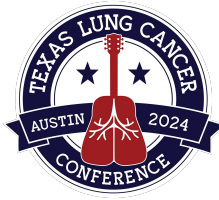


“I think for refractory SCLC—an area of unmet medical need — we have a potent new molecule.”

-Melissa Johnson, MD (2024)

Presented by Melissa Johnson MD at WCLC 2023

Relapsed SCLC: A New Dawn

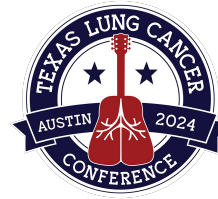


How do we identify new targets for relapsed SCLC, if tissue is limited?

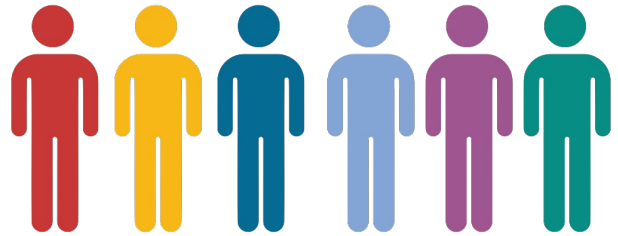
Presented by Melissa Johnson MD at WCLC 2023

Mechanisms of Acquired Chemoresistance in Oncology: SCLC (MACROS) Study Design

PI: Shields
IUSCCC-0828



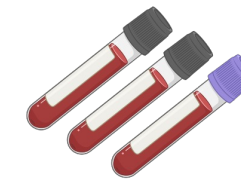
Longitudinal Liquid Biopsies in SCLC



Any patient with diagnosed with SCLC



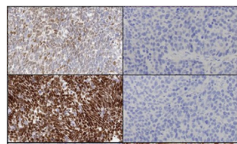
Time of scans



2 Streck
1 EDTA

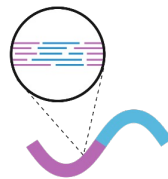
Processed immediately for CTCs
De-ID/ψ/microaliquot in BC²
Batched samples at "events" (POD)

Data analysis:

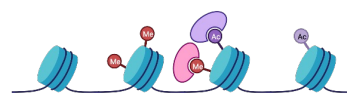


IHC (at diagnosis)

NE subtyping



ctRNA



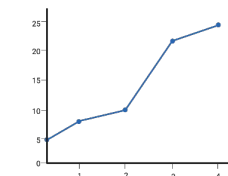
ctDNA

Whole methylome



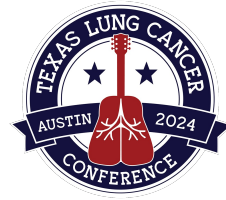
ctDNA

DNA sequencing



CTC enumeration

MACROS Team Members



BIOSPECIMEN COLLECTION & BANKING CORE



Ashley Alto



Myra Miller

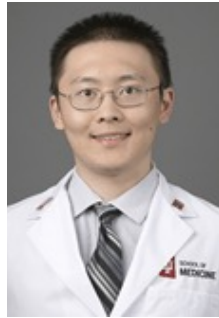


Emily Nelson

*Patient screening/consent
Sample collection/long term storage*



Pam Rockey



Dr. Weston He
IU IM PGY-2

*Clinical Annotation/
RedCap*



Emily Sims
Flow cytometry



Mya Tran,
PharmD

Precision Genomics



Pathology



Dr. Muhammed Idrees
Lee Ann Baldrige

NE Subtypes IHC



Dr. Max Diehn
Stanford

NE Subtypes

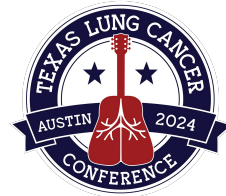


Multi-omics
(DNA, RNAseq, Epigenetics)



Dr. Triparna Sen
Mount Sinai

*Transcriptomic
Immune Signatures*



MACROS: Study Materials Collected to Date

YEAR ONE: April 2023 - Present



First phase of samples submitted for multi-omic analysis

Closing Remarks: Breakthroughs on the Horizon

- **Entering a NEW era of SCLC**, where topotecan is no longer the reluctant SOC
- **Lurbinectedin** is an effective option, even in platinum-resistant SCLC
- **DLL3 BiTEs** show promising & durable responses, *stay tuned!*
- **ADCs** against Trop2, B7-H3, SEZ6 are effective in heavily pretx SCLC
- **Longitudinal liquid biopsies** may inform SCLC plasticity & identify novel targets



Photography Credit: Theresa Colbert
@Goinbrokeranch

